REMARKS

Claims 69-71 and 75-141 were pending. The Examiner withdrew claims 70, 71, 79, 81, and 90-141 as being drawn to a non-elected invention. The Examiner provisionally rejected claim 69 under the doctrine of obviousness-type double patenting; rejected claim 69 under 35 U.S.C. § 112, first paragraph; claims 69, 75-78, 80, and 82-89 under 35 U.S.C. § 112, second paragraph; and claims 69, 75-79, 82-86, and 89 under 35 U.S.C. § 103. Applicants have herein amended claim 69. Applicants' specification fully supports the amended and new claims. Thus, no new matter has been added. Upon entry of the above amendments, claims 69-71 and 75-141 will be pending.

In light of the amendments and the remarks herein, Applicants respectfully request reconsideration and allowance of claims 69-71 and 75-141.

Rejection on the grounds of nonstatutory obviousness-type double patenting

The Examiner rejected claim 69 on the grounds of nonstatutory obviousness-type double patenting over claim 16 of copending U.S. Application Serial No. 10/028,857 (hereinafter, "the '857 application"). In particular, the Examiner alleges that while the present claim is directed to a method of treating a tumor and the '857 application relates to the treatment, prophylaxis, and/or diagnosis of a proliferative disorder, "[c]ertainly, a tumor would qualify as such a disorder."

Applicants respectfully disagree. According to MPEP § 804, paragraph II.B.1.(a):

> if the application at issue is the earlier filed application, only a one-way determination of obviousness is needed to support a double patenting rejection in the absence of a finding: (A) of administrative delay on the part of the Office causing delay in prosecution of the earlier filed application; and (B) that applicant could not have filed the conflicting claims in a single (i.e., the earlier filed) application.

Therefore, for a finding of double patenting under the one-way determination, the claims of the present application must be anticipated by or an obvious variation of the invention as defined in a claim in the copending application. See MPEP § 804, paragraph II.B.1.(a). The claims in the '857 application have been amended such that the presently claimed compounds are not

anticipated nor obvious over those of the '857 application. A copy of the pending claims in the '857 application have been attached for the Examiner's convenience.

Specifically, the compounds of the instant claims are not anticipated by the genus as described in the claims of the '857 application. In the '857 application, position G^1 is limited to alkyl, acyl, silyl, phosphate, or L-T. The present claims, on the other hand, require that the substitution at this position be hydrogen. Therefore, the claims are not anticipated by the claims in the '857 application. Moreover, a further limitation in the '857 claims requires that G^1 be not as it is found in natural vitamin B_{12}. Thus, the '857 application teaches away from having hydrogen in this position as that would render G^1 as it is found in natural vitamin B_{12}. Accordingly, the present claims are not an obvious variation of those found in the '857 application.

Furthermore, Applicants respectfully assert that the double patenting rejection in this, the earlier filed application (by priority), should be withdrawn. According to MPEP § 804, paragraph I.B.1:

> If a "provisional" obviousness-type double patenting rejection (ODP) is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Applicants respectfully assert that all other outstanding rejections have been addressed in the present response to Office Action and therefore, only the "provisional" nonstatutory obviousness-type double patenting rejection remains. Applicants therefore respectfully assert that the Examiner should withdraw the rejection. With respect to the '857 application, Applicants note that they will make the Examiner in the copending case aware of the present application and its prosecution history.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 69, 75-78, 80, and 82-89 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. The Examiner alleges that:

> According to the data in table III (cols 11-12 of USP [5,739,]313), there was some uptake of the [cobalamin] DTPA complex into the tumor cells. But the instant claims are not drawn to a method of achieving uptake into tumor cells. The claims require that reduction in tumor volumes be achieved, or at the very least, that the tumors stop growing. Collins (USP '313) has made no attempt to show that this is possible. Among the various questions to be answered are whether selective uptake of the claimed conjugates is exhibited by tumors in general, or whether only certain tumors will take up the claimed conjugates. See Office Action page 4.

The Examiner further states that "[t]he claims encompass subjecting the afflicted mammal to any and all forms of energy, any and all amounts of energy, and applying that energy to any and all anatomical locations. Surely not all of this is enabled." See Office Action page 6. Overall, the Examiner argues that "[i]n view of the absence of guidance, the absence of working examples, and unpredictability in the oncology field, the skilled oncologist or radiologist would conclude that 'undue experimentation' would be required to practice the claimed invention." See Office Action page 6.

Applicants respectfully disagree. Claim 69, as amended, recites:

> A method of treating a tumor in a mammal comprising:
> a) administering to the mammal an effective amount of a compound of formula I linked to a molecule comprising B-10 wherein X is CN, OH, CH_3, adenosyl, or a molecule comprising B-10; or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable vehicle; and
> b) administering neutron capture therapy comprising subjecting said mammal to thermal neutron irradiation at the site of said tumor for a time and under conditions effective to treat said tumor.

Applicants have fully enabled such a method. The standard for enablement is that the specification teach those of ordinary skill in the art how to make and use the invention without "undue experimentation." See MPEP § 2164.01. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." See In re Wands, 858 F.2d 731 (Fed. Cir. 1988). Moreover, the test for undue experimentation is not "merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine . . . ." See Johns Hopkins University v. Cellpro, Inc., 152 F.3d 1342 (Fed. Cir. 1998). Finally, "[t]he law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art,

for patents are written for persons experienced in the field of the invention." See Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338 (Fed. Cir. 2000).

Applicants respectfully assert that a skilled practitioner can practice the claimed invention without undue experimentation. The specification and the state of the art as of the priority date of the present specification are replete with guidance as to the successful selective uptake of cobalamin conjugates into tumor cells and the administration of boron neutron capture therapy (BNCT) in the selective treatment of tumors. See, e.g., page 1, paragraph 3; page 3, paragraph 29; and references cited therein. In the present Office Action the Examiner argues that for treatment of cancer to be successful, as recited in claim 69, localization at the site of the tumor would be required, but then goes on to state, paradoxically, that while uptake into tumors is achieved (i.e., localization), treatment of the tumors has not been shown. See Office Action page 3. Applicants agree that the present specification does teach uptake (i.e., localization) into tumors. Uptake of cobalamin derivatives into tumors, specifically cobalamin linked to chelating groups, has also been demonstrated *in vivo* in Collins, D.A., *et al., Mayo Clin. Proc.* 75:568-580 (**2000**), a copy of which has been attached hereto for the Examiner's convenience. This publication details the specificity of cobalamin derivatives for tumor uptake in various tumor types, including primary and metastatic breast, lung, colon, thyroid, and sacromatous malignancies.

Further, efficacy of BNCT, once a boron containing compound has been localized in a tumor, is understood and accepted in the field (see, e.g., "Current status of neutron capture therapy," International Atomic Energy Agency (IAEA); IAEA-TECDOC-1223, May 2001; a copy of which is attached hereto). The National Cancer Institute defines boron neutron capture therapy as "[a] type of radiation therapy. The person is given an intravenous infusion containing the element boron, which concentrates in the tumor cells. The person then receives radiation therapy with atomic particles called neutrons from a small research nuclear reactor. The radiation is absorbed by the boron, killing the tumor cells without harming normal cells." Thus, one having ordinary skill in the art, given the present specification and knowledge in the field of

BNCT as of the filing date, would be able to practice the claimed methods, e.g., achieve uptake into tumor cells and administer BNCT, without undue experimentation.

Moreover, Applicants respectfully assert, as stated previously, that the administration and selectivity of boron neutron capture therapy has been known and in use for the selective treatment of tumors for over 50 years, and as such one of ordinary skill in the art would understand how and where to administer neutron capture therapy as stated in the present claims. To further prosecution, however, Applicants have amended claim 69 to include the Examiner's suggested language pertaining to a requirement that administration of thermal neutron irradiation occur at the site of the tumor for a time and under conditions effective to treat the tumor.

Finally, Applicants also respectfully point out that questions regarding specific tumor uptake and cancer treatment validation, for example, are more properly left for agencies other than the Patent and Trademark Office. As set forth in the "Training Materials For Examining Patent Applications With Respect To 35 U.S.C. Section 112, First Paragraph-Enablement Of Chemical/Biotechnical Application," considerations made by the FDA for approving clinical trials and drug products are different from those made by the PTO in determining whether a claim is enabled. See Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("[t]esting for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].") Clearly, validating specific tumor treatment with respect to human clinical diagnostic efficacy is a task more properly within the purview of the FDA rather than the PTO.[1] The fact that one of ordinary skill in the art would perhaps need to perform, for ***FDA approval purposes***, additional validation studies of the ability of the cobalamin derivatives to treat specific

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[1] *See also In re Brana*: "The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.")."

tumors, and the fact that such studies might be considerable, are simply not sufficient to support the Office's contention that the claims are not enabled.

In light of the above, Applicant's respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 69, 75-78, 80, and 82-89 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. The Examiner alleges that claim 69 is indefinite as to the process steps of "administering neutron capture therapy." See Office Action page 7. In particular, the Examiner states that:

> the issue is that of where the dividing line is between a series of steps which would qualify as a 'neutron capture therapy' and a series of steps which would not. It is not clear that claim 69 requires the use of an energy source, or that, if an energy source is required, what the various options might be. For example, if a subject is suffering from pancreatic cancer, would applicants propose irradiating the brain? If a subject is suffering from breast cancer, would applicants propose irradiating the liver?
> See Office Action page 7.

Applicants respectfully disagree. The specification and the state of the art as of the priority date of the present specification provide guidance as to the successful administration and success of boron neutron capture therapy in the selective treatment of tumors. Boron neutron capture therapy has been ***known*** and ***in use*** for the selective treatment of tumors for over 50 years, and as such one of ordinary skill in the art would understand the types of energy source, how, and where to administer neutron capture therapy as stated in the present claims. The Examiner states that claim 69 does not require the use of an energy source nor does it recite specific limitations on where or how long to administer the radiation, but both points are characteristics of BNCT therapy, as recited in the claim ("administrating") and understood by one of ordinary skill in the art. These should not be required as limitations in the claim. By its very definition, as provided by the National Cancer Institute, boron neutron capture therapy is "[a] type of radiation therapy. The person is given an intravenous infusion containing the element boron, which concentrates in the tumor cells. The person then receives radiation therapy

with atomic particles called neutrons from a small research nuclear reactor. The radiation is absorbed by the boron, killing the tumor cells without harming normal cells." One of ordinary skill in the art would not target a location other than that of the tumor to treat a patient, he would understand that the boron would not concentrate in such a location, nor would irradiating such a site provide therapy.

To further prosecution, however, Applicants have amended claim 69 to include the Examiner's suggested language pertaining to a requirement that administration of thermal neutron irradiation occur at the site of the tumor for a time and under conditions effective to treat the tumor.

In light of the above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claim 69, 75-79, 82-86, and 89 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Collins *et al.*, U.S. Patent No. 6,004,533 (hereinafter, "Collins") in view of Schinazi *et al.*, U.S. Patent No. 5,599,796 (hereinafter, "Schinazi"). The Examiner states that:

> Collins discloses compounds in which cyanocobalamin is linked to a diagnostic radionuclide. Collins does not disclose compounds in which cyanocobalamin is linked to boron-10. Schinazi discloses compounds containing boron-10...[but] Schinazi does not disclose that one of those compounds bearing B10 should be cyanocobalamin. However, it would have been obvious to one of ordinary skill to link B10 to cyanocobalamin to achieve the therapeutic benefits asserted by Schinazi.
> See Office Action page 8-9.

Applicants respectfully traverse on the grounds that the Office has failed to establish a *prima facie* case of obviousness. The Office has failed to articulate a reason having a rational underpinning as to why the present claims are obvious given the cited art.

As the Supreme Court recently clarified, for an invention to be obvious under § 103 requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences

between the claimed subject matter and the prior art. Moreover, and importantly, an *explicit rationale* for why one having ordinary skill in the art would have combined the elements in the manner claimed must be set forth. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___ (2007), 2007 WL 1237837 (emphasis added) (hereinafter "KSR"). Indeed, "rejections on obviousness grounds *cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning* to support the legal conclusion of obviousness" (*quoting In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)). *Id.* at 14 (emphasis added). Moreover, the Court acknowledged that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 12. Finally, the "obvious to try" reasoning only applies in "that instance" where two requirements are shown: "there is a design need or market pressure to solve a problem and there are a *finite* number of *identified, predictable* solutions." *Id.* at 17 (emphasis added).

As indicated above, claim 69 recites a method of treating a tumor that includes administering a cobalamin derivative linked to a boron containing compound and administering neutron capture therapy for a time effective for such treatment.

Collins discloses, in part, processes for imaging tumors comprising administering compounds in which cobalamin is linked to a group containing a detectable radionuclide. The process relies upon the fact that tumor cells overexpress cell surface receptors for transcobalamin (a serum protein) which acts as a protein carrier for cobalamin (see, e.g., column 1, lines 57-60, "[a]ll forms of vitamin B_{12} (adenosyl-, cyano-, hydroxo-, or methylcobalamin) must be bound by the transport proteins, Intrinsic Factor and Transcobalamin II to be biologically active"). Thus, by systemically administering to a patient cobalamin linked to an imaging radionuclide, and subsequently imaging all or a portion of the patient's body, a radiologist is able to identify tumors in tissues and organs in the body.

BNCT is not a diagnostic technique. Instead, it is a two step method of therapy that requires (1) administration of boron-10 containing material, and (2) administration of a source of neutrons that causes the decay of the boron-10 with release of destructive energy. Collins does

not address BNCT. Indeed, Collins sets out numerous detectable agents and omits boron-10. See, e.g., column 5, line 61 to column 6, line 20.

Schinazi relates to the treatment of urogenital tumors using lipophilic carborane containing compounds and BNCT. Schinazi teaches that "any boron containing compound that is sufficiently lipophilic to pass through the appropriate urogenital membranes in a quantity high enough to achieve therapy on irradiation with low-energy neutrons can be used." See Abstract. In particular, Schinazi states that "the prostate gland is impermeable to many compounds unless they are lipophilic and delivered ***unbound*** to serum proteins." See Schinazi, column 5, lines 54-56. Thus, Schinazi discloses the use of lipophilic compounds to facilitate entry of boron-10 into tumor cells.

Taken together, these references do not support a case of obviousness because one having ordinary skill in the art would not have been prompted to use cobalamin as a carrier for boron in BNCT. As explained in the background of the present specification and Example 4, cobalamin is delivered to cells in a two step process: (1) the cobalamin binds a transcobalamin transport protein in serum, and (2) the transcobalamin protein binds to a transcobalamin receptor on the surface of the cell. Cobalamin uptake by tumor cells is thus a receptor-mediated event. This is in contrast to uptake mediated by lipophilic transport into lipophilic membranes or materials. Schinazi teaches that increased lipophilicity of the boron-10 bearing compound causes preferential uptake into liposomal materials. Because Schinazi emphasizes the need for a lipophilic boron-10 delivery systems, Schinazi teaches away from a delivery system based upon cobalamin, as cobalamin-based delivery relies upon a receptor-mediated uptake mechanism. Moreover, although Schinazi relates specifically to urogenital tumors, a person of ordinary skill in the art would have not have been disposed to use such a system for other tumors, because he would not have had a reasonable expectation of success in the very tumors Schinazi discusses based on the route of entry required to treat such tumors.

In addition, Schinazi recites in several locations that "any boron containing compound that is sufficiently lipophilic to pass through the appropriate urogenital membranes in a quantity high enough to achieve therapy on irradiation with low-energy neutrons can be used." See

Abstract and column 6, lined 14-17. Schinazi then provides several pages of disclosure relating to how to manipulate the lipophilicity of boron modified compounds. See columns 10-17. Thus, the focus of Schinazi is clearly the use of a lipophilic delivery system.

Cobalamin, however, is well known for its hydrophilicity and water solubility (see, e.g., *The Merck Index* (11th Ed., 1989), which cites the solubility of cobalamin as 1 g in 80 mL of water). Thus, cobalamin is not a lipophilic molecule.

Because Schinazi teaches the necessity of lipophilic boron-10 carriers in BNCT regimens, it teaches away from the use of cobalamin in BNCT.

Accordingly, Applicants respectfully assert that the claims are not obvious, and request withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSIONS

Applicants submit that claims 69-71 and 75-141 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned at the telephone number below if such will advance prosecution of this application.

Please charge Deposit Account 06-1050 for $1020 for the Petition for Extension of Time fee (3 months).

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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